

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/028817

International filing date (day/month/year)
30.09.2004

Priority date (day/month/year)
30.09.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/864, A61K48/00, C07K14/015

Applicant
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/028817

Box No. II Priority

1. ☐ The following document has not been furnished:

- ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

001573600

International application No.
PCT/US2004/028817

AP2004028817 24 MAR 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/028817

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-4(partially),5-7(completely),28-29(partially),30-45(completely)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	7,28-45
	No: Claims	1-6
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-7,28-45
Industrial applicability (IA)	Yes: Claims	1-7,28-44
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

AP20 Rec'd PCT/PTO PCT/US2002/02107
10/573600

Reference is made to the following documents:

- D1: EP-A-1 310 571 (TRUSTEES OF THE UNIVERSITY OF); 14 May 2003
- D2: GAO GUANGPING ET AL: "Adeno-associated viruses undergo substantial evolution in primates during natural infections" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 100, no. 10, pages 6081-6086; 13 May 2003
- D3: WO03/05252 (TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA); 26 June 2003

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- i. Claim 45 comprises a method of treatment and, therefore, relates to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of claim 45 (**Article 34(4)(a)(I) PCT**).

Re Item IV

Lack of unity of invention

- 1. The present application does not comply with the requirements of unity of invention. 88 separate inventions have been identified (for list see international search report). Each of them is an individual solution to the different problems defined below. There is no technical interrelation between these problems and the corresponding solutions.
- 2. The problem to be solved by a first group of inventions is the identification of unknown AAV sequences and their grouping into "clades" (inventions 1-7). The solution to this problem are clades A-F.
The common technical feature of these solutions is that the grouping is based on a mathematical approach using a Neighbor joining heuristic by a bootstrap value of at least 75% per 1000 isolates and a Poisson correction distance measurement of no more than 0.05.
This common concept is not novel because such groups, even though they were not referred to as "clades", have already been described in **D1** (see Figure 2 and

example 2) and also in **D2**..

Moreover, the grouping of AAV sequences lacks an inventive step because it is based on the following known facts and methods:

- AAV is subject to a rapid molecular evolution which results in modified reactivity and tropism of the virus and which resembles the evolution of RNA viruses (see D1 and D2, respectively),
- the rapid molecular evolution is revealed when NHP vp1 sequences of AAV sequences from various primate tissues of clones from the same and from different animals are compared (see D1 and D2, respectively) and
- the grouping is based on techniques and computer programs known to the skilled person as it is pointed out on page 9 (lines 1-8) of the present application.

3. The problem to be solved by a second group of inventions is the provision (isolation) of further non-naturally occurring AAVs (inventions 8-88). The solution to this problem is represented by the various specific AAVs listed in claims 13,17,21,25 and 29 and by AAVs having a capsid with a specific amino acid sequence selected from the AAVs listed in claims 46 and 47. Since at least one member of each clade was already known in the prior art (see description of the present application, page 9, lines 16-24) the various AAV members of each clade represent different solutions to the problem of finding further members of the clades represented by a known AAV. Thus, the 'membership' in a specific clade is not considered a common concept.
4. In the light of the prior art, the special technical features representing the contribution over the prior art of clades A-F are the specific composition of AAVs. The specific composition of members, however, is different for each clade, so that the technical relationship between them required by **Rule 13 PCT** is lacking, and the requirement for unity of invention is not fulfilled. The special technical feature of the various isolated AAVs claimed, is their specific amino acid sequence of the capsid, which is different for each AAV. Thus, the technical relationship between them required by **Rule 13 PCT** is lacking, and the requirement for unity of invention is not fulfilled.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The subject-matter of claims 1-6 is not new in the sense of **Article 33(2) PCT** because of the disclosures made by **D1** anticipate their novelty for the following reason:

D1 discloses a group of AAV, which may also be called a "clade", comprising at least 3 members wherein the members are phylogenetically related and share a capsid with an amino acid identity of at least 85% with the capsid of AAV8 represented by SEQ ID NO: 183 (D1: Figure 2, §126, §182-183, tables 8 and 9).

2. The subject-matter of claim 7 does not involve an inventive step in the sense of **Article 33(3) PCT** for the following reason:

- I. The document D1 is regarded as being the closest prior art to the subject-matter of claim 7 because it discloses an AAV "clade" comprising at least 3 members wherein the members are phylogenetically related and share a capsid with an amino acid identity of at least 85% with the capsid of AAV8 (see above).
- ii. The subject-matter of claim 7 differs from this known "clade" in that it is extended so that it comprises more members.
- iii. The problem to be solved by the present invention may therefore be regarded as the extension of a known "clade".
- iv. The solution proposed in claim 7 of the present application cannot be considered as involving an inventive step because the collection and sequencing of further AAVs and their grouping into clades is based on the following known facts and methods:
 - AAV is subject to a rapid molecular evolution which results in modified reactivity and tropism of the virus and which resembles the evolution of RNA viruses (see D1 and D2, respectively),
 - the rapid molecular evolution is revealed when NHP vp1 sequences of AAV sequences from various primate tissues of clones from the same and from different animals are compared (see D1 and D2, respectively), and
 - the grouping is based on techniques and computer programs known to the skilled person as it is pointed out on page 9 (lines 1-8) of the present application.

- v. Thus, it would have been obvious to the person skilled in the art to repeat the methods disclosed in D1 in order to extend the AAV "clade" constructed around AAV8. Moreover, D1 also includes an incentive to the skilled person because it points out that it is very useful to isolate novel AAVs since the "tropism of each new vector is favourable for in vivo applications".
3. Moreover, the grouping of AAVs into clades lacks a technical aspect and, therefore, cannot be considered a technical contribution to the art. It is a mere presentation of information. A patent application, however, must provide a technical solution to a technical problem. Thus, the subject-matter of claims 1-7 is not patentable (**Rule 67.1(v) PCT**).
4. The subject-matter of claims 28-45 does not involve an inventive step in the sense of **Article 33(3) PCT** for the following reason:
- i. The document **D3** is regarded as being the closest prior art to the subject-matter of claims 28-45 because it discloses several AAV serotypes including one termed AAV9 which shares 81% identity at the genomic level with hu.14/AAV9 of the present application (D3: SEQ ID NO: 1)
 - ii. The subject-matter of claims 28-45, i.e. hu.14/AAV9 differs from the serotypes disclosed in D3 in its specific genomic sequence.
 - iii. The problem to be solved by the present invention may therefore be regarded as the identification of an alternative AAV serotype.
 - iv. The solution proposed in claims 28-45 of the present application, i.e. hu.14/AAV9, cannot be considered as involving an inventive step because the present application does not demonstrate an unexpected or surprising effect associated with hu.14/AAV9. In the absence of surprising or distinguishing properties, however, no inventive step can be acknowledged.

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 45 with regard to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 45 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details